Life Stress and Cervical Squamous Intraepithelial Lesions in Women With Human Papillomavirus and Human Immunodeficiency Virus

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Objective: Human immunodeficiency virus (HIV)-infected women are at risk for cervical intraepithelial neoplasia (CIN) and cancer due to impaired immunosurveillance over human papillomavirus (HPV) infection. Life stress has been implicated in immune decrements in HIV-infected individuals and therefore may contribute to CIN progression over time. The purpose of this study was to determine whether life stress was associated with progression and/or persistence of squamous intraepithelial lesions (SIL), the cytologic diagnosis conferred by Papanicolaou smear, after 1-year follow-up among women co-infected with HIV and HPV. **Method:** Thirty-two HIV-infected African-American and Caribbean-American women underwent a psychosocial interview, blood draw, colposcopy, and HPV cervical swab at study entry. Using medical chart review, we then abstracted SIL diagnoses at study entry and after 1-year follow-up. **Results:** Hierarchical logistic regression analysis revealed that higher life stress increased the odds of developing progressive/persistent SIL over 1 year by approximately seven-fold after covarying relevant biological and behavioral control variables. **Conclusions:** These findings suggest that life stress may constitute an independent risk factor for SIL progression and/or persistence in HIV-infected women. Stress management interventions may decrease risk for SIL progression/persistence in women living with HIV. **Key words:** HIV, squamous intraepithelial lesions (SIL), human papillomavirus (HPV), stress, psychoneuroimmunology (PNI), women.

AIDS = acquired immune deficiency syndrome; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HAART = highly active antiretroviral therapy; HGSIL = high-grade SIL; HIV = human immunodeficiency virus; HPV = human papillomavirus; LES = Life Experiences Survey; LGSIL = low-grade SIL; NKCC = natural killer cell cytotoxicity; SIL = squamous intraepithelial lesions.

HIV-infected women have high prevalence, incidence, and persistence rates of both human papillomavirus (HPV) infection and cervical intraepithelial lesions (CIN) (1–6). HIV-infected women also experience high rates of CIN recurrence (7) and treatment complications (8). Although recent studies have not observed high-grade CIN and invasive cervical carcinoma with great frequency in HIV-infected women (2, 6), Maiman et al. (9) found that cervical cancer was the most common acquired immune deficiency syndrome (AIDS)-related malignancy among HIV-infected women in New York City from 1987 to 1995. They also reported that cervical cancer was more likely to recur despite adequate therapy and was associated with a greater risk of death.

Low socioeconomic status African-American women living with HIV may be at especially high risk for CIN progression, recurrence, and treatment complications. African-American women are disproportionately affected by HIV (10) and HPV infections (4) and have the second highest cervical cancer mortality rates in the United States (11). Therefore, primary and secondary prevention of CIN are crucial to maximizing the health and quality of life of minority women co-infected with HIV and HPV.

HPV infection, impaired immune functioning, and behaviors such as smoking have been identified as risk factors for CIN in HIV-infected women. However, virtually no research has examined the possible role of psychosocial factors, such as life stress. Life stress and other psychosocial factors such as depression have been implicated in the reactivation of latent viruses (12–14), immune decrements in both HIV+ men and women (15, 16), faster progression to AIDS in HIV+ men and women (17–19), and more advanced CIN in HIV- women (20). The purpose of the present study was to determine whether life stress was associated with the progression and/or persistence of squamous intraepithelial lesions (SIL), the cytologic diagnosis conferred by Papanicolaou smear, in African-American and Caribbean-American women living with HIV and HPV[1].

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[1] For the purposes of this paper, CIN and SIL will be used interchangeably.

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MATERIALS AND METHODS

Participants were 32 HIV-1 seropositive African-American, Haitian, Jamaican, and Bahamian women between the ages of 15 and 50 enrolled in a National Cancer Institute funded study of psychosocial, viral, and immune risk factors for CIN. Participants were recruited from an immunology clinic in the Department of Obstetrics and Gynecology at the University of Miami. This study was conducted in accordance with the rules and regulations of the Human Subjects Committee of the Institutional Review Board at the University of Miami School of Medicine.

Inclusion criteria included one abnormal Papanicolaou smear in the 2 years before study enrollment, a CD4+CD3+ cell count ≥ 150 cells/mm^3, and fluency in English. Exclusion criteria included past or current clinical AIDS (ie, Category C) diagnosis (21), a history of high-grade SIL (HGSIL) or cervical cancer, hysterectomy, treatment for SIL in the year before enrollment, and intravenous drug use in the 6 months before enrollment.

We used a prospective study design. At study entry, participants completed informed consent and underwent a psychosocial assessment interview, peripheral venous blood draw, and colposcopy and HPV cervical swab. A 10-item abbreviated version of the Life Experiences Survey (LES) (22) was used to measure stressful life events. The LES has been used successfully in prior cross-sectional research examining the association between psychosocial factors and cervical dysplasia (23). In the present study, we used a modified 10-item version of the LES. This shortened version of the LES was developed by researchers at the University of Miami in the early 1990s to assess the unique stressors of HIV+ women of color in obstetric-gynecology settings, particularly HIV+ postpartum women. To this end, focus groups were convened to determine the most frequent and salient life events listed on the full 57-item LES for this specific population. Focus group responses revealed that stressors associated with the peripartum period, such as changes in eating and sleeping habits, pregnancy, addition of a new family member, and an outstanding personal achievement (eg, "being a good mom") were cited as most frequent and salient. Other stressors included changing a work situation, residence, and church activities. These were often cited as indirectly caused by or complicated by pregnancy or childbirth. Deaths of family members and close friends were also cited as frequent and salient. The LES-10 comprised these items. Although not all of our participants in the current study were postpartum, we elected to use the LES-10 due to the similarities between our sample and focus group respondents in socioeconomic status, health concerns, and recruitment setting (special immunology obstetrics-gynecology clinic). A secondary benefit of using this instrument was decreased participant burden, an important concern when working with hard-to-access populations.

For each event that occurred in the past year, participants rated its impact from "extremely negative" (-3) to "extremely positive" (+3). An average subjective impact score for negative life events experienced in the 6 months before enrollment was computed. This stress score equaled the sum of the impact scores for all negatively rated events divided by the total number of negative life events experienced. If a participant did not experience a negative event listed on the LES-10, she was assigned a life stress score of "0," or "no impact." Higher life stress scores indicated higher impact of negative life events (ie, 0 = no impact; 1 = slightly negative; 2 = moderately negative; 3 = extremely negative).

The distribution of lymphocyte phenotypes was determined by flow cytometry at study entry as described in detail by Ironson et al. (24). Given the relationship between greater immunosuppression and risk for SIL promotion in HIV-infected women (6), we measured the decline in CD4+CD3+% as a possible control variable. CD4+CD3+% after 1-year follow-up was abstracted using chart review.

At study entry, a colposcopic examination was conducted by two colposcopy-trained nurse practitioners according to standard colposcopy protocol (25). Before the application of acetic acid solution, an HPV cervical swab was collected for detection and subtyping of HPV. HPV detection and subtyping utilized dot blot (DB) hybridization analysis as described previously by Byrnes et al. (26). Briefly, this procedure allowed for the detection of HPV types 6/11/42/43/44 ("6/11"), the types conferring low risk for SIL progression, and types 16/18/31/33/35/45/51/52/56 ("16/18"), the types conferring intermediate and high risk for SIL progression (3). For the purposes of this study, we operationalized risk for SIL progression as presence of HPV types 16/18. Presence of these types was coded as "1," while absence of these types (including presence of HPV 6/11) was coded as "0."

We used medical chart review to follow SIL diagnoses prospectively for 8 to 16 months based on cytology[2]. This time frame was selected because our prospective data collection was linked to patient care, and patients averaged approximately one Papanicolaou smear every 8 months[3].

SIL outcome was operationalized in terms of whether the participant experienced the progression and/or persistence of SIL at 1-year follow-up. If a participant experienced the progression or persistence of SIL at 1 year, she was assigned a "1" for the outcome variable, while a "0" was assigned for participants who remained free of SIL or regressed to no SIL over this period.

To control for the possible effects of immunosuppression on SIL progression over the follow-up period (6), we also followed CD4+CD3+% prospectively for 6 to 18 months. We utilized this time frame because our prospective data collection was linked to patient care, and participants averaged approximately one T-cell subset analysis every 6 months.

We began by conducting independent-samples t tests and χ^2 analyses between progression and/or persistence at 1-year follow-up and demographic (ie, age, income, education); viral (ie, presence of HPV 16/18); behavioral (eg, cigarette smoking and medication use); immune (ie, CD4+CD3+% decline); and gynecological (eg, number of genital herpes simplex virus outbreaks) control variables relevant to SIL. We then used hierarchical logistic regression analysis to predict progression and/or persistence after 1 year from life stress. If a control variable was related to progression and/or persistence after 1 year ($p \leq .10$), it was entered as a covariate in the regression equation before entry of life stress. Covariates were entered in blocks with similar variables. The predictor of interest, subjective impact of negative life events in the 6 months before study entry ("life stress"), was added in the last block.

RESULTS

Demographic Characteristics

The 32 participants included African-American (78%), Haitian (13%), Bahamian (3%), and Jamaican (6%) women with a mean age of 28.2 years (SD = 6.3).

[2] We utilized a histopathologic diagnosis for one participant who did not have a cytologic SIL diagnosis during follow-up. Exclusion of her data did not alter the findings in this paper.

[3] One participant had 5 months between SIL diagnoses at study entry and follow-up. Exclusion of her data did not alter the findings in this paper.

The vast majority described themselves as single/never married (78%) and reported having one current sex partner (71%). The mean level of education was a high-school degree (mean years of education = 11.6, SD = 1.7), and 72% of the participants reported a yearly income of less than $10,000. Eighty-seven percent (N = 27) of the women reported having at least one child, and 59% reported parturition in the past year. The mean time since last delivery was 3.5 years (SD = 6.0). One participant became pregnant during the 1-year follow-up period. She did not carry the pregnancy to term.

Health Status

Clinical and immunologic status. At study entry, the mean time since HIV diagnosis was 3.0 years (SD = 2.1), and all participants were in the asymptomatic or symptomatic (pre-AIDS) phase of HIV infection. Thirty-five percent of the participants reported experiencing at least one current HIV-related symptom at baseline. The mean CD4+CD3+ cells/mm^3 at baseline was 526.9 (SD = 254.3). One participant had a CD4+CD3+ cell count below 200 cells/mm^3, 13 (43%) had counts between 200 and 500 cells/mm^3, and 16 (57%) had counts greater than 500 cells/mm^3. The mean baseline CD4+CD3+ percentage was 27.2% (SD = 9.3) with a statistically significant decline to 23.7% (SD = 10.3) after 1 year [$t(31) = 3.5$, $p = .002$].

HPV status and squamous intraepithelial lesions. Fifty percent of the women were infected with HPV 16/18 at baseline. Seventy-five percent had no SIL at baseline, whereas 25% had (low-grade SIL) LGSIL. At 1-year follow-up, 78% had no SIL, 19% had LGSIL, and 3% had HGSIL. Sixty-three percent remained free of SIL at baseline and 1 year, while 15% regressed from LGSIL at baseline to no SIL at 1 year. This group was designated the "no SIL at follow-up" group. In contrast, 22% either developed new SIL or showed evidence of persistent LGSIL or HGSIL at 1-year follow-up. This group was designated the "progressed or persistent SIL at follow-up" group.

Health-Related Behaviors

At study entry, 16 participants (50%) were not on antiretrovirals or protease inhibitors, while 7 (22%) were on one antiretroviral ("monotherapy"), and 9 (28%) were on double or triple combination therapy. Only two women on combination therapy reported taking a protease inhibitor. Twenty-eight percent of women had at least one diagnostic procedure (ie, cervical biopsy and/or endocervical curettage)[4] for SIL during the follow-up period. No participants had treatment (ie, LEEP procedure or cone biopsy) for CIN during the follow-up period.

Eleven women (34%) reported cigarette smoking at baseline. Of the women who smoked, the average number of cigarettes smoked in the month before baseline interview was 325.5 (SD = 237.3) or approximately four packs per week. Only eight women (25%) reported alcohol use and three (9%) reported marijuana use in the month before study entry. No participants reported use of crack cocaine in the month before study entry, although eight (26%) reported a prior history of crack cocaine use.

Life Stress

Forty-four percent (N = 14) reported no negative impact of life events in the past 6 months, 19% (N = 6) reported a slightly negative impact, 18% (N = 6) reported a moderately negative impact, and 19% (N = 6) reported an extremely negative impact. The most common negatively rated life event was the death of a close friend or family member. Thirty-one percent (N = 10) reported being aversively impacted by a death in the past 6 months. The frequency of each negatively rated life stressor is listed in Table 1.

Relations Between Progression/Persistence of SIL and Control Variables

Table 2 presents the means and standard deviations (SDs) of continuous control variables by SIL status at 1-year follow-up (ie, progressive and/or persistent SIL vs. regressive and/or absent SIL). Independent-samples t tests revealed that women with progressive and/or persistent SIL at 1 year experienced greater declines in CD4+CD3+% [$t(30) = 2.36$, $p = .03$] and reported higher negative life stress scores before study entry [$t(30) = 2.27$, $p = .03$]. Decline in CD4+CD3+% was retained as a control variable in further analyses. In contrast to other research (27), the number of cigarettes smoked in the month before study entry was not significantly associated with SIL status.

Likelihood ratio tests between SIL status at 1-year follow-up and highly active antiretroviral therapy (HAART) status, income bracket, and presence of HPV 16/18 revealed that only the presence of HPV 16/18 was significantly associated with progression and/or

[4] Unlike treatment procedures, such as LEEP procedure or cone biopsy, neither of these diagnostic procedures would be expected to affect the risk of SIL progression/persistence during follow-up.

TABLE 1. Frequency of Negatively-Rated Life Stressors Experienced in the Past 6 Months by HIV+ Women in an Obstetric-Gynecology Setting

Life Stressor	Frequency
Death of a family member	6
Death of a close friend	4
Major change in eating habits	3
Major change in sleeping habits	3
Change in a work situation	3
Pregnancy*	3
Major change in church activities	2
Change in residence	2
Addition of a new family member	0
Outstanding personal achievement	0

* Of the three women who reported pregnancy as a negative life stressor in the past 6 months, only one carried the pregnancy to term.

persistence of SIL at 1 year [χ^2 (2) = 4.97, p = .03]. This was retained as a control variable. HAART usage was marginally associated with regression and/or absence of SIL at 1-year follow-up [χ^2 (2) = 5.37, p = .07]. HAART usage was retained as a control variable in further analyses as a conservative measure due to its documented relationship with SIL (28). Income was unrelated to SIL status at 1-year follow-up.

Predicting Progression/Persistence of SIL with Life Stress

Our regression equation contained three blocks of variables. The first block included biological control variables (ie, HPV 16/18, declines in CD4+CD3+%); and the second block included behavioral control variables (ie, antiretroviral usage). Life stress was entered in the third block. After controlling for biological and behavioral control variables, hierarchical logistical regression revealed that life stress accounted for 27% of the variance in progression and/or persistence of SIL at 1 year. Higher life stress increased the odds of developing progressive and/or persistent SIL over 1 year by approximately nine-fold (95% CI = 1.07–69.08)[5]. The overall model was significant [χ^2 (4) = 18.36, p = .001] (Table 3).

The possibility existed that several life stressors, namely major changes in eating habits and sleeping habits, could be manifestations or consequences of HIV disease progression. In addition, although no study to date has shown that pregnancy is associated with significantly elevated risk for mortality or AIDS incidence in HIV+ women, pregnancy carried to term is associated with immunologic changes (29) that could possibly alter risk for SIL progression/persistence. As a conservative measure, we eliminated negativity ratings associated with major changes in eating and sleeping habits. Of the three women who reported pregnancy as a negative life event in the 6 months before study entry, only one carried the pregnancy to term. To eliminate the possibility that pregnancy-induced alterations in immune functioning may have influenced risk for SIL at follow-up, we removed this participant from our logistic regression analysis. With our revised life stress score and removal of this participant, hierarchical logistical regression revealed that life stress accounted for 26% of the variance in progression and/or persistence of SIL after 1 year. Higher life stress increased the odds of developing progressive and/or persistent SIL over 1 year by approximately seven-fold (95% CI = 1.00–45.14). The overall model was significant [χ^2 (4) = 18.14, p = .001].

[5] We were initially concerned that multicollinearity between our predictors may have produced inflation of the standard error of the regression coefficients, leading to wide confidence intervals. However, we tested for this and found that the tolerance associated with life stress was 0.93, indicating that only a small percentage of the variance in life stress was accounted for by other independent variables in the equation. The wide confidence intervals are likely due to our small sample size.

DISCUSSION

For many years, life stress has been posited and examined as a possible cofactor in the initiation and promotion of neoplastic processes, particularly those that are virally mediated and therefore immunogenic (12). Life stressors have been associated with the reactivation of latent viruses, such as herpesviruses (12–14), immune decrements in HIV+ men and women (15–16), faster progression to AIDS in HIV+ men and women (17–19), and more advanced cervical intraepithelial neoplasia in HIV-seronegative women (20). There is substantial evidence that CIN is initiated by HPV, a latent DNA virus that is commonly sexually transmitted. Psychosocial factors, such as life stress, may be associated with impaired immunosurveillance over HPV infection and increased risk for CIN progression. Among women co-infected with HIV and HPV, preliminary evidence exists that psychosocial factors are associated with lower natural killer cell cytotoxicity (NKCC) and percentages of cytotoxic/suppressor T cells (23), two immune markers linked to viral and neoplastic control (30).

Therefore, in the present study, we evaluated the effects of life stress on the progression and/or persistence of squamous intraepithelial lesions in African-American and Caribbean-American women living with human immunodeficiency virus and human papillomavirus. In doing so, we observed high rates of oncogenic HPV infection and SIL prevalence at study

TABLE 2. Means and Standard Deviations of Potential Control Variables by SIL Status at 1 Year

Potential Control Variable	Progressive/Persistent SIL Group		Regressive/Absent SIL Group		*t*	*df*	*p* Value (2-tailed)
	Mean	SD	Mean	SD			
Age (yrs)	28.00	6.68	28.24	6.34	−0.09	30	0.94
Education (yrs)	11.86	1.95	11.58	1.67	0.37	29	0.72
No. of HIV-related symptoms at study entry	0.14	0.38	0.88	1.45	−1.31	29	0.21
Length of time since HIV diagnosis (yrs)	3.14	2.67	2.91	1.94	0.26	29	0.80
No. of sex partners at study entry	0.57	0.53	0.83	0.48	−1.24	29	0.23
No. of episodes of unprotected sex in month prior to study entry	0.00	0.00	2.42	10.18	−0.62	29	0.54
Age at first coitus (yrs)	16.43	2.82	15.90	1.76	0.61	30	0.55
No. of cigarettes smoked in month prior to study entry	50.00	65.57	129.20	229.82	−0.89	30	0.38
No. of Pap smears in 24 months prior to study entry	2.57	1.90	2.84	1.03	−0.50	30	0.62
CD4+CD3+% decline over 1-year follow-up (log transformed)	−7.93	3.60	−2.36	5.79	−2.40	30	0.03*
No. of HSV-2 outbreaks over 1-year follow-up	0.20	0.45	0.08	0.27	0.80	28	0.44
No. of drinks of alcohol consumed in month prior to study entry	1.43	2.30	3.60	11.26	−0.50	30	0.62
No. of times of marijuana usage in month prior to study entry	0.00	0.00	3.70	13.17	−0.73	30	0.47
Negative life stress impact score [0 (none) − 3 (extremely negative)]	1.96	1.02	0.88	1.13	2.27	30	0.03*

* $p \leq .05$.

TABLE 3. Predicting Progression and/or Persistence of SIL After 1 Year from Life Stress in the Past 6 Months

(Step Number) Predictor	Wald Statistic	Odds Ratio	95% CI	*p* Value
(1) Biological variables				
Presence of HPV 16/18 at study entry	2.07	.18	.02–1.88	.15
Decline in CD4+CD3+% during 1-year follow-up	2.86	.81	.64–1.03	.10
(2) Behavioral variable				
Antiretroviral medication use at study entry[a]	.73	.50	.10–2.46	.40
(3) Psychological variable life stress[b]	4.08	8.58	1.07–69.08	.05

$N = 32$. Significance of model, χ^2 (4) = 18.36, $p = .001$.

[a] 0 = no use of antiretrovirals; 1 = use of 1 antiretroviral; 2 = use of 2 or more antiretrovirals.

[b] Average impact rating of all negatively rated events in the past year as measured by a modified 10-item version of the Life Experiences Survey (Sarason et al., 1979) (0 = no impact or no negatively rated life events; 1 = slightly negative; 2 = moderately negative; 3 = extremely negative).

entry, which is consistent with other research (3). Fifty percent of women were infected with oncogenic HPV types, and 25% of women had SIL at baseline. These numbers are higher than those found by Minkoff et al. (3) (HPV prevalence: 38.5%; abnormal Papanicolaou smear prevalence: 22.5%), perhaps because we specifically recruited women with at least one recent abnormal Papanicolaou smear from an immunology obstetric and gynecology clinic. Contrary to other published research (31), however, only 22% had SIL that progressed and/or persisted over the year. This may be due to several factors. First, our sample was relatively healthy because we excluded women with AIDS-related opportunistic infections and CD4+CD3+ cell counts below 150 cells/mm^3. The overall health of our sample may have created an unfavorable environment for SIL progression and persistence. Second, our reliance on Papanicolaou smears may have underestimated the percentages of women with SIL (32–33). Third, given the components of the study (eg, psychosocial interview) and time commitment required, selection bias may have resulted in a sample that was more adherent with medical recommendations (eg, colposcopies, medication) or more knowledgeable or

concerned about their health. Fourth, because these women were attending an immunology clinic because they had been identified as especially high risk for SIL, they represented patients receiving medical care more aggressive than normal throughout the follow-up period. Despite these potential sources of bias, we were able to identify a subgroup who still revealed evidence of disease progression and/or persistence at follow-up.

As predicted, women experiencing life stress in the 6 months before study entry had a seven-fold risk of developing progressive/persistent SIL 1 year later. This finding held after we controlled for the presence of oncogenic HPV types, declines in CD4+CD3+% over follow-up, and antiretroviral medication usage. This is the first study to our knowledge to demonstrate a longitudinal relationship between stress and SIL in women living with HIV.

The most common negative life stressor in the sample was the death of a close friend or family member. Multiple AIDS-related bereavements are common experiences for HIV+ women (34). Bereavement is associated with a rapid decline of CD4+CD3+ cell count (35) and decrements in NKCC and lymphocyte proliferate responses in HIV+ gay men (36). Psychosocial interventions for HIV+ bereaved men, conversely, exhibit beneficial effects on immune status, neuroendocrine functioning, and distress in HIV+ men (37–39). Few, if any, studies have examined the impact of bereavement on health outcome in HIV+ women. The present data may be among the first to suggest that bereavement is a risk factor for cervical dysplasia, an AIDS-related and gender-specific condition.

Life stress may be associated with SIL progression and persistence in this sample through neuroendocrine and immune pathways or through health behavior pathways. Life stress may cause decrements in natural immunity (eg, NKCC) and/or cell-mediated immunity (eg, CD4+CD3+ cells, CD8+CD3+ cells) through elevations in glucocorticoid hormones, such as cortisol (34–35, 40–41). Decreases in these components may affect immunosurveillance over HPV infection and may allow SIL to persist or progress (36, 42).

Life stress may also affect SIL persistence through behavioral pathways. High levels of life stress may interfere with self-care behaviors, which are vital to health maintenance for women living with HIV. For instance, women with high levels of life stress and distress may have difficulty following through with medical recommendations for Papanicolaou smear screenings, colposcopy, and antiretroviral medication usage (37–40, 43–46), thus leading to SIL progression and/or persistence.

Although the present findings do not reveal the pathways through which stress is associated with SIL, they do suggest that HIV+/HPV+ women who are experiencing life stress may benefit from psychosocial assessment and counseling as an adjunct to standard medical care. Obstetric and gynecology practitioners may consider referring highly stressed patients to group-based cognitive-behavioral stress management interventions (41, 47). Within a supportive group atmosphere, such interventions emphasize increasing awareness of the effects of stress and changing appraisals of stressful situations in order to impact mood, behavior, and interpersonal relationships. Furthermore, these interventions seek to improve coping skills, social support, anger management, and assertiveness skills. Prior work has demonstrated potentially beneficial psychological, hormonal, and immunologic changes in HIV+ individuals participating in this form of intervention (42–44, 48–50). The present research broaches the possibility that honing these skills may buffer SIL progression and/or persistence in women living with HIV and HPV.

The present study has several limitations. The low sample size may have produced unstable findings and lack of generalizability. Replication with a larger sample is needed. In addition, the LES-10 does not represent all of the potentially important life events experienced by HIV+ women, such as poverty, racism, domestic violence, and unsafe neighborhoods. It also contained several items that could be manifestations of HIV disease progression (eg, changes in eating habits) or could potentially alter risk of SIL progression/persistence (eg, pregnancy). Future research in this area should utilize life stress measures that provide greater variation in type, chronicity, and severity of life events and less potential for confounding with disease status. Given the fact that much of our data were collected before HIV viral load was routinely measured in HIV+ individuals, we were unable to control for the possible effects of HIV viral load on SIL progression/persistence. Future research should examine the possibility that life stress affects SIL through decreases in HAART adherence and increases in HIV viral load. Furthermore, the prospective design of our research necessitated the use of chart review to obtain SIL diagnoses. The quantity and quality of follow-up data in charts are confounded with illness factors and access to medical care, which may have biased our data in unknown ways. We also did not have histopathologic confirmation of SIL at study entry or follow-up. Reliance solely on Papanicolaou smears for follow-up may have underestimated the percentages of women with SIL at follow-up (32–33). Finally, this research would be better served by gauging lifetime history of cigarette smoking (eg, through pack-years of smoking), rather than cigarette smoking in the month before study en-

try. Pack-years of smoking may be related to progression/persistence of SIL unlike recent cigarette smoking. Despite these limitations, it seems plausible that psychosocial assessment and stress management may emerge as important components of primary care and gynecologic treatment for women living with HIV and HPV.

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